in the circulation or released from tissue into the circulation as the result of tissue injury. One of these peptides, or some other thus far uncharacterized basic peptide, may be involved in the pathogenesis of the membrane transport abnormalities demonstrable in cystic fibrosis.

In addition to its abnormalities in membrane transport of electrolytes, cystic fibrosis is characterized by an excessive mucus production throughout the body. Extensive research has demonstrated only an increase in macromolecular components normally present in the mucous secretions but no unique abnormal glycoprotein molecule.[1] It is possible that the excessive mucus is indeed a result of the defect in membrane transport, but this remains to be substantiated.

In spite of these helpful new clues, the metabolic riddle of cystic fibrosis remains unsolved. When the factors which can influence metabolism of electrolytes or of glycoproteins or both have been clearly identified, one must ask whether their presence is the result of a missing enzyme which normally degrades them, or of a missing normal inhibitor, or of a genetically-determined overproduction of a normal substance. Spirited collaboration of geneticist, biochemist, physiologist, immunologist and clinician will be required to follow the present promising clues to their final answer.

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Bone Disease in Chronic Renal Failure — Questionably the Result of Our "Successful" Treatment of Uremia

THE LAST FEW YEARS have seen a remarkable increase in the clinical investigative interest in the disordered divalent ion metabolism and bone disease associated with chronic renal failure. This increased interest is directly related to the fact that as the lives of patients with this disorder have been greatly prolonged by transplantation, clinically severe osteodystrophy and soft tissue calcification have become life-threatening problems in an alarming number of cases. It is deeply distressing that we are able to treat uremia successfully and to rehabilitate the patient only to be confronted, at times, with the most florid forms of metabolic bone disease, and a type of vascular and soft tissue calcification capable of causing severe ischemic necrosis of skin, subcutaneous tissue, and phalanges. We and others have observed that as the duration of chronic dialysis increases, regardless of the composition of the dialysate, the frequency of bone disease and soft tissue calcification also increases. In our own series the incidence of radiological evidence of bone disease increased from 18 percent at one year to 92 percent at the end of three years. This is not an unusual experience in major dialysis centers.

Despite these pessimistic observations it is clear that the recent acceleration in clinical and laboratory investigation into the problems of renal osteodystrophy are bringing us closer to a proper understanding of its cause, diagnosis and treatment. The present issue of CALIFORNIA MEDICINE contains Dr. Frank Muldowney's review entitled "Metabolic Bone Disease Secondary to Renal and Intestinal Disorders." Dr. Muldowney has given us an example of the type of challenging and provocative concepts and inquiries now being made in this field. He discusses the similarities and differences between the biochemical changes and metabolic bone disease of chronic renal failure and those of intestinal disorders associated with calcium, phosphorus and vitamin D deficiency. He suggests that phosphate depletion, which may be common to

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both, may be the fundamental cause of the osteomalacia component of renal osteodystrophy, while the osteitis fibrosa component is due to the prolonged (years) secondary hyperparathyroidism. Dr. Muldowney suggests that the hypocalcemia responsible for the parathyroid hyperplasia in chronic renal failure is due to small but progressive increments in serum inorganic phosphorus, which in turn are secondary to a gradual reduction in glomerular filtration rate (GFR) and renal mass. It is quite clear that renal osteodystrophy represents a varied histologic picture with osteomalacia and osteitis fibrosa predominating, but frequently with varying degrees of true bone atrophy (osteoporosis) and ostesclerosis also present.[1] Furthermore, the clinically and histologically (bone biopsy) predominant lesion in any given patient may vary depending on the age of the patient, the duration and severity of his renal failure, his long-term nutritional state and the nature of his treatment, including, of course, chronic dialysis.[2] In fact, one form of therapy may tend to correct or ameliorate a given skeletal lesion, while aggravating another. For example, "very successful" large-dose antacid therapy may lower serum phosphorus to normal and thereby at times return serum calcium to normal. The latter may decrease the pronounced hypersecretion of parathyroid hormone and lessen the degree of osteitis fibrosa or parathyroid bone disease. Antacid therapy lowers serum phosphorus by inhibiting the intestinal absorption of phosphorus and causing phosphorus depletion. The latter, as stressed by Dr. Muldowney, can aggravate or cause osteomalacia, with a failure of available bone matrix to mineralize.

Bone atrophy, or osteoporosis, when present may be due to aging, chronic calcium and protein deficiency, plus varying degrees of inactivity. It should be stressed that the therapeutic diet of the azotemic patient is almost always deficient in calcium, phosphorus and protein. The exact cause of osteosclerosis (hyperostosis, per Dr. Muldowney), or more mineralized bone per unit volume,[1] is unknown. It may represent aberrant calcification of excess osteoid or the fibrous matrix of osteitis fibrosa. If in any given patient with chronic renal disease it was possible to study the entire skeleton, varying amounts of each of these histologic lesions would be seen.

It is becoming increasingly clear that the abnormal metabolism of divalent ions and metabolic bone disease may begin very early in patients with chronic renal disease. Minimal reductions in glomerular filtration rate may be associated with hypocalciuria, defective absorption of calcium from the gastrointestinal tract, slight hypocalcemia with normal, or even low, serum phosphorus,[3] and a relatively high renal clearance or low tubular reabsorption (TRP) of phosphorus.[3] This is the classic biochemical pattern produced by a vitamin D deficient or resistant state with secondary overactivity of the parathyroid glands. In confirmation of the latter, elevated levels of parathyroid hormone, as measured by radioimmunoassay, have now been detected in the plasma of patients with less than 20 percent reduction in GFR.[4] Unfortunately, information on bone histology and the biochemical response to vitamin D in these early cases is not yet available.

Although Dr. Muldowney has emphasized the role of phosphate depletion and early small increases in serum phosphorus as playing fundamental etiologic roles in osteomalacia and osteitis fibrosa in chronic renal disease, the overall evidence seems to be more in favor of the early development of an acquired vitamin D resistant state which in turn is responsible for: (1) impaired absorption of calcium from the gastrointestinal tract; (2) defective mineralization of osseous matrix, or osteomalacia; (3) impaired response of the skeleton to parathyroid hormone. It has been clearly shown experimentally[5] that a vitamin D effect on the skeleton is essential for the normal response of the latter to parathyroid hormone. Therefore, a greater amount of parathyroid hormone is necessary to maintain a normal serum calcium. Factors 1 and 3 would be primarily responsible for the early development of hypocalcemia *in the absence of* hyperphosphatemia. However, as was emphasized by Dr. Muldowney, any rise in serum phosphorus would tend to lower the serum calcium further. As long as the latter is maintained, hyperplasia and hypersecretion of the parathyroids will continue. After many years the parathyroid glands may enlarge as much as 50 to 100 times, and the circulating levels of parathyroid hormone may exceed 1,000 times the normal concentration.[4] Osteitis fibrosa appears in a florid form, serum calcium returns to, or even goes slightly above, normal; and due to the simultaneous hyperphosphatemia the $Ca^{++} \times PO_4^{\equiv}$ product attains a level where soft tissue calcification is inevitable. At this point the parathyroid glands are so massively enlarged that they continue to

secrete excessive amounts of hormone despite normocalcemia, and if hypocalcemia develops again these huge glands secrete much more hormone than normal for any given degree of hypocalcemia. It is probable that true autonomy of the parathyroid glands does not exist in chronic renal failure, the apparent autonomy being simply the result of the mass of secreting parathyroid tissue.[6] However, when this "autonomous" state does exist almost all forms of therapy, short of subtotal or total parathyroidectomy, may either aggravate the bone disease or decidedly increase soft tissue calcification. We are then confronted with the complete picture of severe sustained secondary hyperparathyroidism in chronic renal failure—that is (1) serum calcium usually normal, rarely elevated; (2) hypercalcemia after phosphate restriction; (3) hyperphosphatemia, which may respond poorly to phosphate restriction or hemodialysis; (4) osteitis fibrosa or subperiosteal bone resorption; (5) soft tissue calcification; (6) increased calcium content of skin; (7) pruritus unresponsive to adequate dialysis; (8) postdialysis diffusible or ionized calcium in serum greater than its concentration in the dialysate; (9) elevated alkaline phosphatase, or (10) bone pain (uncommon).[6]

It was pleasant to note Dr. Muldowney's discussion of magnesium depletion in humans and its possible role in impairing the end organ response to parathyroid hormone, and the ability of mild hypermagnesemia to inhibit parathyroid secretion.[7] While we have stressed the role of the vitamin D resistant state as the fundamental "lesion" contributing to the early over-activity of the parathyroid gland, it is possible that magnesium deficiency could have the same result.

It is clear from Dr. Muldowney's and the present discussion that the clinician confronted with a disordered divalent ion metabolism and bone disease in chronic renal failure must make the most critical evaluation before proceeding with any specific form of therapy. One approach may improve a given biochemical abnormality while leading to a further deterioration of the skeleton or more soft tissue calcification.

As in all research or clinical investigation, as an increased number of clinicians and investigators become involved in gathering data and searching for the correct answers, the contributions increase in a geometric manner and it is that we are now at this phase. It seems likely that the most important answers with respect to the pathogenesis, diagnosis and treatment of these serious disorders will be available to us very soon.

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Medicine and the New Human Condition

THE HUMAN CONDITION seems to be undergoing a change. The cause is easy to understand. The energy of man's machines is doing much of the work which used to require his muscles, and a lot more. This has happened only recently. The result seems certain to be a truly new human condition to which human beings must adjust.

A curious paradox has developed which may be one of the root causes of many present day tensions. On the one hand inanimate power has reduced the need for human or even animal labor. Leisure has increased and affluence is unprecedented. A new expectation, even a demand for the opportunity of self-expression and individual fulfillment has become an insistent force in our society. There is real restiveness when these expectations and demands are not instantly met. On the other hand the refinements of scientific and technologic progress which make this very human dream seem so close to attainable exact their price. The more it frees of man's time, muscle